Case Series
Sciences of Pharmacy

Hypertriglyceridemia Induced Acute Pancreatitis: A Learn from New Cases

Ramandeep Singh, Ranjodh Jeet Singh, Satinder Kakar, Jasmeet Kaur

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Abstract: An increased risk of morbidity and mortality is associated with acute pancreatitis (AP) brought on by hypertriglyceridemia (HTG). It is essential to locate the root cause as soon as possible and give those affected the attention they need. The treatment plan includes efforts to lower blood triglyceride levels and supportive care. HTG-induced AP has a similar clinical course to people with other types of acute pancreatitis. However, HTG-induced AP patients have significantly higher clinical severity and associated consequences. As a result, therapy and preventing sickness recurrence depend on a correct diagnosis. At the moment, there are no acknowledged standards for the treatment of HTG-induced AP. Some therapy approaches that effectively decrease serum triglycerides include fibric acids, apheresis/plasmapheresis, insulin, heparin, and omega-3 fatty acids. Following acute phase care, lifestyle modifications, including dietary and drug therapy, are essential for long-term HTG-induced AP control and relapse prevention. To create complete and efficient HTG-induced AP treatment guidelines, more study is required.

Introduction

Acute Pancreatitis

Acute pancreatitis is a common condition with various causes. Hypertriglyceridemia, an uncommon but well-known cause of AP, can have life-threatening effects if it is severe enough. In 1–7% of individuals with 1,000 mg/dL or higher triglyceride levels, HTG as a cause of AP occurs (1). Additionally, alcohol and gallstones are the two most common etiologies (2). A systemic inflammatory response is sparked by the pancreatic acinar cells, leading to the AP inflammatory illness. With a high risk of death, this inflammatory process may cause multisystem organ failure and pancreatic necrosis. Early detection and timely treatment of AP are required to reduce the risk (3).

Cause of Acute Pancreatitis

The cause of AP can be categorized as follow (3):

Cholelithiasis

The most frequent cause of AP in the United States is chronic pancreatitis, which should be investigated in anyone displaying the symptoms. To be the initial cause, radiologic imaging must demonstrate choledocholithiasis or cholelithiasis without any other risk factors. It is necessary to assess the patient's liver enzyme panel as well. Irritation of the gall bladder wall, tiny stones, and sludge have all been associated with idiopathic AP. Endoscopic retrograde cholangiopancreatography (ERCP) has been shown to reduce overall mortality and morbidity in patients with ductal obstruction in those who exhibit symptoms of ductal obstruction associated with cholelithiasis. Clinical signs of ductal obstruction include an increase in total bilirubin on imaging, aspartate aminotransferase, alanine aminotransferase, or ductal dilatation.

Magnetic resonance cholangiopancreatography (MRCP) does not support therapeutic therapy for AP. Hence its diagnostic utility is constrained. While ERCP may also be utilized for therapeutic purposes, MRCP is only used for diagnostic purposes.

Alcohol Use

Additionally, heavy alcohol use can result in AP. Alcohol-induced AP is the medical term for AP brought on by excessive alcohol use (greater than 80 milliliters in a day).

Hypertriglyceridemia

Although HTG is relatively uncommon, it is the third most prevalent cause of AP, accounting for 7% of all cases. In most cases, it may be challenging to establish hypertriglyceridemia as the cause of AP. The two most frequent causes of AP, alcohol and gallstones, can also result in acquired HTG, which is mild to moderately elevated. The secondary effect of alcohol usage and gallstone obstruction on lipid metabolism is increased triglyceride levels. Gallstone blockage of the bile ducts causes a rise in triglyceride levels, which in turn causes triglyceride levels to rise.

The increase in VLDL (very low-density lipoprotein) levels in the liver and adipose tissue cause a rise in triglyceride levels in the blood. People with high blood triglyceride levels who do not have gallstones or alcohol-induced pancreatitis can develop HTG-related pancreatitis.

Hereditary Pancreatitis

It's critical to rule out hereditary pancreatitis in those who have experienced multiple episodes of AP. Adults over the age of 30 frequently get AP from hereditary pancreatitis. Due to their higher risk, monitoring these people for pancreatic adenocarcinoma is vital. Patients with hereditary pancreatitis are also more likely to develop chronic pancreatitis, which can result in fibrosis and abnormalities in the pancreatic ducts, eventually leading to pancreatic exocrine and endocrine insufficiency. Genetic testing and ocular examination for signs of acute or chronic pancreatitis can be used to identify patients with hereditary pancreatitis.

Pancreatic Duct Variants and Anomalies

Due to abnormalities in the pancreatic duct, AP that returns frequently needs surgery. Congenital abnormalities in the pancreatic duct that might not be discovered until adulthood can be seen with abdominal imaging. If you suspect a problem with your pancreatic ducts, the MRCP is the best initial test to perform.

Autoimmune Pancreatitis

Idiopathic duct-destructive pancreatitis, also known as autoimmune pancreatitis, is a clinical diagnosis that shows an enlarged pancreas and constriction of the primary pancreatic duct, a condition known as autoimmunity. Jaundice, weight loss, and epigastric discomfort are all signs of autoimmune pancreatitis.

Pharmaceutical Agents

Statins, selective serotonin reuptake inhibitors, and metformin are among the drugs that might trigger an AP. AP caused by medication can range from mild to severe.

Hypertriglyceridemia

Serum triglyceride levels rise as a result of HTG. Fredrickson Groups I, IV, and V are the most common types of HTG, and they all have one thing in common: an elevated level of chylomicron and VLDL (4). Hyperlipidemia is an epiphenomenon that has been associated with AP. HTG or chylomicronemia may account for up to 7% of all cases of pancreatitis. Table 1 shows the clinical diagnosis criteria for HTG. The most frequent type of AP is not due to alcohol or gallstones (2). When triglyceride level in a body is high, AP and associated cardiovascular issues are more likely to occur. When a patient exhibits AP symptoms due to HTG, serum triglyceride concentrations over 1,000 mg/dL suggest severe HTG (3). AP rates rise in response to increases in TG concentration. AP is unlikely to happen if the TG level is less than 1000 mg/dL (5). On the other hand, there is no connection between high cholesterol levels and AP. When high triglyceride readings, low-density lipoprotein cholesterol (LDL cholesterol), apolipoprotein B (ApoB), and total cholesterol are present, the condition is referred to be dyslipidemia and is more severe than acute biliary (TC) (6).

The prevalence of HTG in adults ranges from one in ten to one in thirty (HTG). Genetic (primary) and environmental factors can both contribute to elevated triglyceride levels (TG) (secondary). In 2% of cases, autosomal recessive, monogenic familial chylomicronemia syndrome can result in primary severe HTG (TG >10 mmol/L) (FCS, former Type I). Although secondary factors and polygenic (mixed HTG, formerly Type V) determinants are present in most severe HTG patients, most of these cases are multifactorial. The genetic propensity to the disease is as complex in mild-to-moderate cases of HTG (former Type IV, Type IIB and Type III). Alcohol and a positive-energy balanced diet are two environmental factors that might result in high triglyceride (TG) levels, along with obesity, uncontrolled diabetes mellitus, renal illness, pregnancy, hypothyroidism, and drugs (such as estrogens, retinoids, and β-blockers) (7).

Table 1. Criteria for clinical diagnosis of hypertriglyceridemia.

Degree of hypertriglyceridemia	Serum triglycerides (mg/dL)
Mild	150-199
Moderate	200–999
Severe	1,000–1,999
Very severe	≥ 2,000

Etiology of Hypertriglyceridemia

Hypertriglyceridemia causes can be divided into two categories: primary causes and secondary causes. By the main one, HTG is made worse. TG triglyceride

accumulates substantially, which can cause pancreatitis, even while the secondary (acquired) form alone does not produce a significant amount of HTG, which might be a risk factor for AP. An abnormality in regulating the body's synthesis of TG-rich VLDL is the most frequent cause of elevated TG levels. This can lead to either an increase in VLDL levels alone (type IV hyperlipidemia) or an increase in VLDL levels together with chylomicrons (type V hyperlipidemia). The most common causes of endogenous HTG are obesity, high caloric intake, alcohol usage, estrogens or certain medications, and obesity (8). Knowing the etiology can help doctors select long-term treatment plans that work and address specific risk factors associated with HTG causes (3).

Primary Cause (Familial Hypertriglyceridemias)

Pancreatitis is linked to hyperlipidemia of types I, IV, and V. Adults are more likely to have type V or IV abnormalities if they have familial hyperlipidemia and pancreatitis. The majority of faults are Type V. Type I and type V can exist when pancreatitis develops without a secondary factor, but type IV almost always needs a secondary factor to elevate TG levels drastically.

Familial chylomicronemia, also known as Type I hyperlipidemia, is a rare autosomal recessive condition passed down from one generation to the next. The most frequent cause, lipoprotein lipase (LPL) insufficiency or apo C-II deficiency, almost always presents in early childhood. The amount of fat consumed affects the degree of chylomicronemia and the fasting HTG in people with familial hyperlipoproteinaemias. Familial mixed hyperlipidemia and familial HTG are more likely to manifest in adulthood than familial chylomicronemia. The genetic mutations that lead to these disorders are unknown, but family members must be examined for abnormalities in lipoproteins to obtain a clinical diagnosis. Not only can TG levels increase in cases of familial combination hyperlipidemia, but so can cholesterol levels (8).

Secondary Causes

Diabetes Mellitus

A diabetic patient who has received subpar care has HTG-induced pancreatitis. Lipoprotein analysis has revealed elevated VLDL levels (type IV hyperlipidemia). People with hyperlipidemic pancreatitis are more prone to develop the disorder when diabetes is poorly managed or treated. Type 1 diabetics have lower lipoprotein lipase activity because the generation of the enzyme depends on insulin. Due to their hyperinsulinemia and insulin resistance, type 2 diabetics have higher levels of TG production and lower levels of TG clearance from the bloodstream (8).

Pregnancy

The third trimester is the stage of pregnancy when TG levels are at their greatest. If present, chylomicronemic syndrome and severe HTG can result from an unbalanced lipid profile and cause pancreatitis. Increased adipose tissue lipolysis, which gives the liver substrates for TG synthesis, and decreased lipoprotein lipase activity, which leads to insufficient TG clearance from the body, are two potential causes. It is strongly encouraged to obtain a fasting lipid profile as early in pregnancy as feasible because AP during pregnancy can directly impact both the mother and the unborn child (8).

Estrogen-based Oral Contraceptives

Exogenous oestrogen therapy for postmenopausal women and birth control pills can potentially increase TG levels. Reduced post-heparin lipolytic activity leads to either an increase in endogenous TG synthesis due to higher insulin concentrations or a decrease in TG elimination. If a woman already has impaired lipoprotein metabolism, she is more likely to develop pancreatitis when using exogenous oestrogens. Recently, it was shown that 39% of the women who were sent for testing for high HTG (>750 mg/dL) were receiving exogenous oestrogen. According to the authors, exogenous oestrogen replacement should be avoided if blood TG levels are greater than 300 mg/dL or 750 mg/dL, respectively. Before beginning oestrogen replacement medication, the fasting serum TG level should be assessed. It should also be tested often while the drug is being administered. Oral estrogens alone are more likely to cause HTG adverse effects than transdermal estrogens, oestrogen injections, and oestrogen and progesterone combos. With more recent low-dose estrogens, HTG is less likely than with earlier estrogens (8).

Medications

A variety of medications have the potential to significantly increase HTG when a preexisting lipoprotein abnormality is present, which can result in AP. Exogenous estrogens, beta-blockers, diuretics, and anti-HIV medications are all taken orally; it should be noted. If the problematic medications are stopped, TG levels will recover to pre-treatment levels (8).

Alcohol

Cameron et al. were the first to examine the link between alcohol and HTG. They discovered that most alcoholic patients with HTG admitted for AP had a preexisting impairment in lipoprotein metabolism (8).

Due to the increased amount of FFAs in forming TG or VLDL, alcohol use reduces hepatic oxidation of free fatty acids (FFAs). This is because of the same metabolic route. Alcohol consumption has also been linked to an increased risk of developing HTG. Alcohol consumption alone would not be able to raise TG levels

enough to cause AP. Even when paired with a high-fat diet, the amount of TG is not increased by alcohol use alone; rather, an abnormality in lipid metabolism may amplify the effects of both alcohol consumption and a high-fat diet (4).

Pathophysiology of Hypertriglyceridemias Causing Acute Pancreatitis

AP and HTG have been associated for over 150 years (4). The exact way that HTG produces AP is still unknown. Based on animal model studies, it is well-accepted that excessive TG metabolism by pancreatic lipase to free fatty acids (FFA) results in pancreatic cell damage and ischemia (3). Pancreatic lipase hydrolyzes TG in and around the pancreas, causing the acinar cells to leak out and produce a lot of free fatty acids. Free fatty acids are harmful and can injure capillaries and acinar cells if they are unbound. Capillary obstruction, ischemia, and acidosis are all caused by increased chylomicron concentration in the pancreatic capillaries. In this acidic environment, free fatty acids activate trypsinogen and start AP. This idea was supported by experimental studies that used TG and free fatty acid (oleic acid) infusions to cause pancreatic edema, weight gain, and increased blood amylase. The pancreas preparations received these injections. When free fatty acids were administered, the damage was similar but occurred more quickly. High TG levels in pancreatic capillaries show that ischemia solely affects the pancreas and does not damage other organs. Genetic changes, including CFTR and ApoE gene mutations, have been connected to HTG-AP. Further research is necessary to determine the precise etiology of HTG-AP (5).

Prevalence of Hypertriglyceridemia in the General Population

Serum lipid distributions in US individuals have been studied throughout time by the NHANES research. Serum TG values between 150 and 200, 200 to 500, and 500 to 2000 mg/dL were identified in 14.2, 16.3, and 1.7% of US adults, respectively, using NHANES data from 2001 to 2006. There was a problem with the study since it didn't break down the 500-2000 mg/dL group into subgroups for TG >1000 mg/dL prevalence. A very small percentage of patients with severe HTG (i.e., >2000 mg/dL) was found, and these patients were removed from future research. Men, middle-aged, and more likely to have diabetes, chronic renal illness, and other abnormalities in blood lipids than women were among the subjects with TG levels greater than 500 mg/dL (high non-HDL and low HDL) (9).

Physiology of Lipids and Hyperlipidemia

Molecularly, lipoproteins are composed of the same fundamental components but in varying amounts. Ultracentrifugation may divide them into five groups, from the least dense and biggest to the tiniest and densest. Lipoproteins have the following components (8):

1. Chylomicrons
2. Very-low-density lipoproteins (VLDL)
3. Intermediate-density lipoproteins
4. Low-density lipoproteins (LDL)
5. High-density lipoproteins (HDL)

While cholesterol is the primary lipid in LDL, The main lipid found in VLDL is tri-glyceride. VLDL and chylomicron catabolic products, intermediate-density lipoproteins have equivalent levels of both lipid components.

Plasma TG can be produced from either an endogenous or an exogenous source. Dietary intake makes up the vast bulk of TG intake in healthy individuals. Enterocytes in the gut break down and absorb dietary fat, converting the chylomicrons it contains into TG-containing ones. Chylomicrons are transferred to the venous system via the thoracic duct system after being secreted into lymphatic vessels. The plasma contains apoprotein C-II, also referred to as apo C-II, which is a cofactor for the enzyme lipoprotein lipase (LPL).

TGs are created in the liver and released as VLDL, which is then eliminated. Chylomicron and VLDL transit through and are stored in muscle and adipose tissue under lipoprotein lipase (LPL) regulation. All parenchymal tissue cells secrete LPL, which travels to endothelial cells in nearby capillary beds and hydrolyzes TG, chylomicrons, and VLDL to release fatty acids used by muscle cells for cellular oxidation and by adipose tissue for TG resynthesis and storage. Most people's serum chylomicrons start to emerge 1 to 3 hours after eating and disappear within 8 hours. TGs are virtually always present at TG values of more than 1,000 mg/dL.

Hyperlipoproteinemia is characterized by over the 95th percentile of the reference population's plasma lipids or lipoproteins levels, which indicates an overabundance of one or more macromolecules that transport lipoproteins in the blood. Classifications of hyperlipidemia states are as follows (8):

1. Primary (hereditary or sporadic genetic disorder of metabolism)
2. Secondary (associated with an identifiable disease or condition and is reversible with control or eradication of that disease or condition)

Natural History of Hypertriglyceridemia Pancreatitis

Controlling blood sugar and other secondary risk factors is critical in patients with HTG pancreatitis natural history. Fortson et al. found that 44 percent of

individuals with HTG pancreatitis had a history of previous bouts.

Despite strict diet and treatment regimens, only one patient in a group of 17 patients with HTG pancreatitis had recurrences over a 42-month follow-up period. Among 35 patients with Type V hyperlipoproteinemia, those with bouts of pain only (n=8) and those with pain plus pancreatitis (n=11) were more likely to be younger and had higher mean TG levels (5865 vs. 2573 mg/dL) than those with no pain (n=16). Treatment (diet, medicine, or jejunoileal bypass) significantly reduced the number and severity of pain episodes (HTG abdominal crises) and the frequency of pancreatitis attacks throughout a follow-up period of 1-11 years.

Although the link between HTG and recurring bouts of pancreatitis is well-known, little research has been done on whether HTG might develop chronic pancreatitis (CP). In individuals with type I and V hyperlipidemia, chronic pancreatitis (CP) has been documented. HTG is likely to play a role in the recurrence of attacks and the eventual shift to CP in alcohol-addicted individuals (chronic pancreatitis) (9).

Diagnosis of HTG as a cause of AP: The finding that a patient with AP had blood TG levels over 1000 mg/dL supports the theory that HTG is to blame for the condition. If no other evident cause of AP can be established, or if the measurement of TG has been delayed, a TG level of 500 mg/dL should raise serious concerns. A serum TG level should be tested within 24 hours after a presentation (as near to the commencement of pain or presentation as feasible) since the inflow of TG-rich chylomicrons into the bloodstream declines quickly during fasting. This is why it's critical to check TG levels as soon as possible. Hypocaloric intravenous fluids reduce serum TG levels by cutting off VLDL production from the liver. After 72 hours of fasting, most patients with HTG-induced AP whose TG levels were greater than 1750mg/mL[2] had a considerable drop in TG levels. After two weeks, most of these patients had TG levels slightly over the normal upper range.

If the TG level is not examined soon after admission, the identification of HTG as the cause of AP or Recurrent Acute pancreatitis (RAP) may be delayed or missed entirely. Patients classified as idiopathic may have HTG as the underlying cause. High suspicion in an appropriate clinical environment and thorough monitoring of blood TG levels during AP attacks is essential to detect HTG-infected individuals. HTG can be detected by fasting serum TG levels at a patient's follow-up examination following oral diet initiation.

In line with the guiding principles of the American College of Gastroenterology, AP is diagnosed when at least two of the following three symptoms are present (4):

1. Epigastric abdominal pain.
2. Higher than three times the upper limit of normal levels of enzymes in the blood (amylase or lipase).
3. AP(9) or morphological indicators of AP on abdominal computed tomography are compatible with radiological imaging.

Treatment of Hypertriglyceridemia-induced Acute Pancreatitis

To lower blood triglycerides to less than 500 mg/dL or even 200 mg/dL, medical therapy aims to boost lipoprotein-lipase activity and promote chylomicron breakdown (1). The numerous treatment options for AP caused by HTG are as follows (10).

1. Insulin drip
2. Heparin
3. Plasmapheresis (PEX)

Initially, vigorous intravenous hydration, dietary restriction, and pain management treat AP caused by HTG. Insulin drips, plasmapheresis, and heparin injections are all options for treating high triglycerides (3). Figure 1 depicts the suggested treatment line for AP caused by high TG.

Insulin Drip

In HTG-induced AP treatment, insulin drip therapy can be administered safely and successfully. Continuous intravenous insulin infusion treats HTG with insulin drip (1). If you're concerned about your triglyceride levels, this may help. Increased peripheral lipoprotein lipase activity aids in the breakdown of the excess triglycerides in the bloodstream Lipoprotein lipase (LPL) activity is boosted by insulin (10). Glucose testing is performed every 30 minutes to every hour, and the insulin dosage is 0.1 to 0.3 U/kg/h by continuous infusion. Low-density lipoprotein metabolism and chylomicron breakdown are both accelerated by insulin (3).

Heparin

The lipoprotein lipase, which breaks down triglycerides, is increased by heparin. Heparin, like insulin, boosts lipoprotein lipase at first, decreasing this enzyme's activity with time. Long-term hazards include an increase in the release of harmful components from triglycerides, impaired triglyceride metabolism, and hepatic storage of triglycerides, as demonstrated by studies. As a result, triglyceride levels may rise, leading to an increased risk of bleeding (3).

Plasmapheresis

Faster reduction of levels to < 500 mg/dL is achieved with plasmapheresis, which physically eliminates triglycerides from the blood. Patients with high triglyceride levels will have some of their plasma removed and replaced with a colloid solution. Plasmapheresis has a major advantage over insulin in treating HTG in terms of speed. On the other hand, the plasmapheresis treatment costs a lot of money. Patients at a higher risk of problems or showing evidence of organ failure or necrosis may benefit from this treatment (3).

Plasmapheresis has been shown to assist five individuals with AP caused by HTG during pregnancy, whereas five others have not benefitted from plasmapheresis. Reductions in the inflammatory response and length of hospitalization were achieved with plasmapheresis (from 100% to 28.6%). It is recommended that patients with HTG-induced AP not undergo plasma exchange because of the lack of data from randomized controlled trials, just one controlled study, 12 case reports, and 33 individual case reports. Centrifugal and double membrane filtration procedures can be used to exchange therapeutic plasma in these individuals. Because triglycerides clog the filters in centrifugal systems, they appear more effective than the double membrane approach (6).

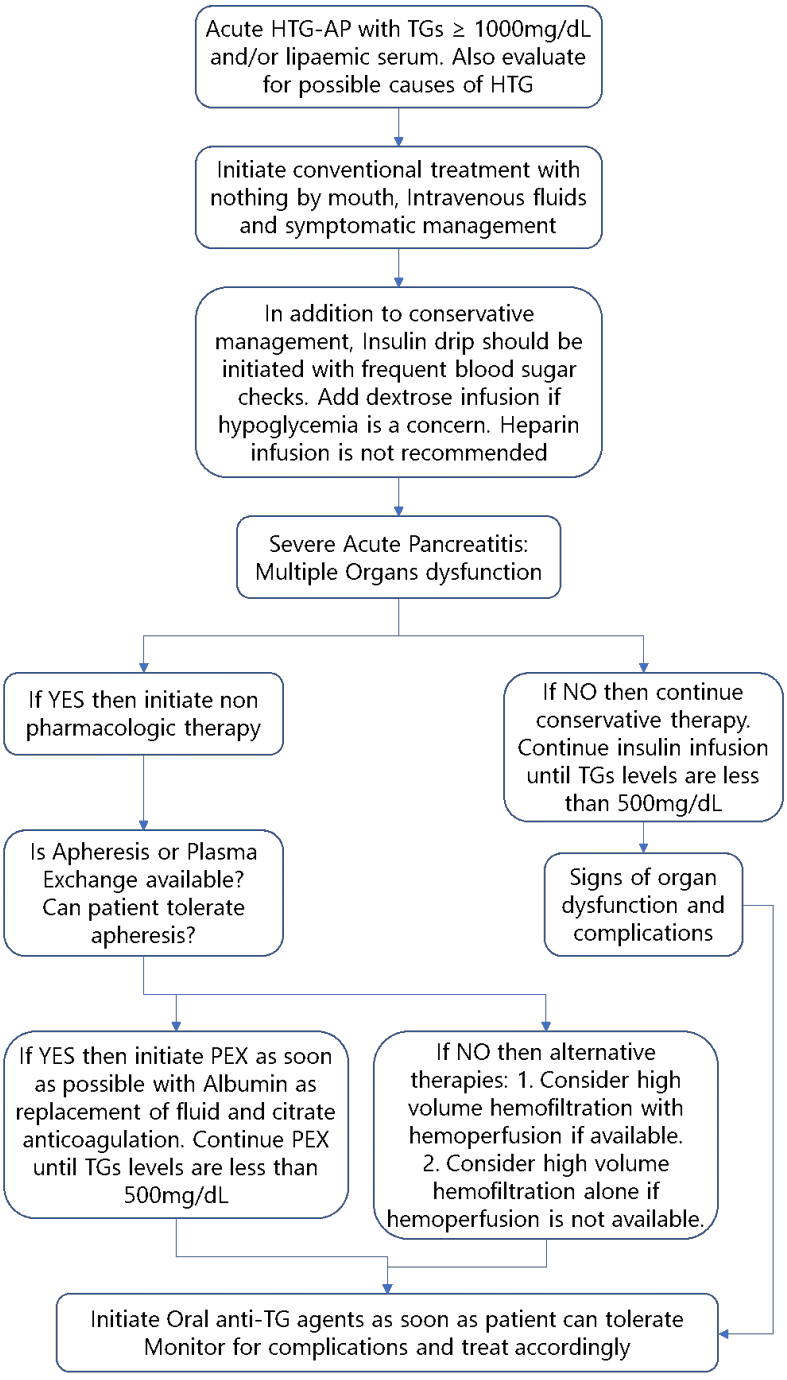
Acute HTG-AP with TGs ≥ 1000mg/dL and/or lipaemic serum. Also evaluate for possible causes of HTG
Initiate conventional treatment with nothing by mouth, Intravenous fluids and symptomatic management
In addition to conservative management, Insulin drip should be initiated with frequent blood sugar checks. Add dextrose infusion if hypoglycemia is a concern. Heparin infusion is not recommended
Severe Acute Pancreatitis: Multiple Organs dysfunction
If YES then initiate non pharmacologic therapy
If NO then continue conservative therapy. Continue insulin infusion until TGs levels are less than 500mg/dL
Is Apheresis or Plasma Exchange available? Can patient tolerate apheresis?
Signs of organ dysfunction and complications
If YES then initiate PEX as soon as possible with Albumin as replacement of fluid and citrate anticoagulation. Continue PEX until TGs levels are less than 500mg/dL
If NO then alternative therapies: 1. Consider high volume hemofiltration with hemoperfusion if available. 2. Consider high volume hemofiltration alone if hemoperfusion is not available.
Initiate Oral anti-TG agents as soon as patient can tolerate Monitor for complications and treat accordingly

Figure 1. Proposed algorithm for treatment of HTG-AP (5).

Prevention of Recurrent Pancreatitis

NCESP defines three levels of triglyceride elevation: a) mildly raised 150–199 mg/dL; b) moderately elevated 200–499 mg/dL; and c) elevated 500 mg/dL. According to current research findings, an increase in triglyceride concentrations exceeding 1000 mg/dL may increase the risk of developing AP and should be treated with fibrates, fish oil, and nicotinic acid. First-line treatment for AP prevention includes a reduction in fat and carbohydrate consumption as well as the use of fibrates. As triglyceride levels fall below 500 mg/dL, AP can be prevented (6).

Diet

General measures and control of secondary factors: Treatment of people with HTG over the long term often includes addressing secondary issues such as alcohol abstinence, weight loss, withdrawal of offending medication, diabetic management, and hypothyroidism. In those with HTG, researchers have shown that limiting alcohol consumption decreases TG levels.

Nutritionists must provide patients with nutritional guidance as a component of their treatment plan. Exercising and losing weight are important components of a healthy diet and should be highlighted together. In the absence of weight loss, Step I and II diets increase plasma TG levels. On the other hand, step I and II weight loss programs positively affect TG levels and other lipoproteins. TG levels fall as a result of weight reduction.

In the case of type I hyperlipidemia, the majority of therapy is a fat restriction in the diet. Fat consumption should be lowered to 10%-15% of total caloric intake (including saturated and unsaturated fats) (8).

Fish Oil Supplements

Normalizing TG levels using fish oil supplements or using it in conjunction with medication works well. Endogenously produced TG-rich lipoproteins, VLDL, and intermediate-density lipoproteins are all reduced in a dose-dependent manner by these drugs. In healthy people and patients with hyperlipidemia, plasma TG levels are lowered, especially when VLDL concentrations are increased, and diet and exercise have not been able to diminish considerably elevated TG levels. Eicosapentaenoic acid and docosanoic acid, as well as other minor fatty acids, are the active components in fish oil. Eicosapentaenoic acid is principally responsible for its TG-lowering properties. N-3 fatty acids have an effective dosage of more than one gram daily. In hypertriglyceridemic individuals, a daily dosage of 3 to 4 g reduces plasma TG by around 30% to 50%. The therapeutic decrease in TG levels necessitates using n-3 fatty acid supplementation.

Keeping a close eye on weight gain and a tendency to haemorrhage with fish oil supplements is important. Additionally, fishy odor and gastrointestinal distress are possible adverse effects (8).

Medications

Table 2 shows the ways to prevent recurrent pancreatitis. Secondary hyperlipidemia should be investigated and treated before starting any medication in any patient. Dietary restrictions on fat consumption are the foundation of therapy for type I hyperlipidemia. Drug treatment, on the other hand, may be necessary to reduce VLDL production and prevent severe HTG.

Table 2. Prevention of recurrent pancreatitis.

Assess underlying disorder (familial, secondary)
Weight loss, abstinence from alcohol, withdrawal of offending medication, diabetes, and hypothyroidism are all secondary issues to be managed.
Dietary interventions: a low-fat diet, fish oil supplements
Lipid-lowering drugs: fibric acid derivatives, niacin +/− statins

Gemfibrozil, fenofibrate, and clofibrate are all fibric acid derivatives, or fibrates, which lower TG levels and enhance HDL levels at the same time. For primary HTG, these are the first-line medicines. In the treatment of lipid disorders, gemfibrozil is commonly prescribed. Fibric acid derivatives have a variety of ways of lowering TG levels. The lipoprotein lipase activity of fibrates has been shown to increase. Fibers also reduce hepatic TG production by boosting hepatic fatty acid intake, lowering neutral lipid exchange between VLDL and HDL (cholesterol-ester and TG), and promoting reverse cholesterol transport, all of which lead to increased LDL particle elimination. To avoid pancreatitis, long-term usage of fenofibrate may stabilize triglyceride levels (10).

HMG-CoA (hydroxy-3-methyl glutaryl coenzyme A) reductase inhibitors are the most widely given medications for HTG (sometimes called statins). They are very popular in preventing coronary artery disease for those with high total cholesterol, LDL cholesterol, and mild to moderate TG increases. Commercially accessible statins include atorvastatin, simvastatin, pravastatin, lovastatin, and fluvastatin. Myopathy is a common side effect of statins when used with fibrates, despite being well tolerated.

By lowering VLDL production, niacin lowers TG levels. LDL and HDL cholesterol levels are boosted as a result. Hepatotoxicity, glucose intolerance, and hyperuricemia are all symptoms of gastric distress, and flushing and pruritus are some of the more common niacin adverse effects that have been documented.

The use of antioxidants and plasma exchange

treatment in individuals with familial HTG and chronic pain has recently been proven beneficial. Plasma exchange has also been useful in lowering lipid and pancreatic enzyme levels and improving symptoms of AP. By removing only big molecular weight complexes (lipoproteins) from plasma, lipoprotein apheresis reduces infection and bleeding risk by preserving immune globulins, albumins, and clotting factors (8).

Case Reports

Case 1

Patients were referred to the hospital with epigastric pain and vomiting that persisted for three days before admission. They had uncontrolled type II diabetes mellitus and a BMI of 39 kg/m2. The patient's auscultation indicated no abnormalities in the lungs or heart, as well as no abdominal distention, epigastric discomfort, or guarding, in addition to a heart rate of 135 beats per minute, a respiratory rate of 32 beats per minute, and a blood pressure of 88/46 millimeters of mercury. With an APACHE II score of 14, she was admitted to the ICU and received fluid resuscitation and other supportive treatments. A scan of her abdomen revealed that her pancreas was encased in fat and was enlarged. Her ABG revealed severe anion gap metabolic acidosis. The TG concentration was 9,230 milligrams per deciliter, and an ultracentrifuge test showed that the blood was extremely lipemic. Table 3 shows the lab findings. She had never had pancreatitis or gallstones before, nor had she abused alcohol or narcotics. The patient's severe AP and diabetic ketoacidosis, which were brought on by severe HTG (SHTG), were treated with enteral fenofibrate and other supportive therapies. Plasmapheresis was started once it became apparent that she needed vasopressors to keep her blood pressure under control.

Table 3. Initial laboratory investigations.

Laboratory investigation	Value
Haemoglobin (g/dL)	14.1
Total leucocyte count (×103/µL)	14.5
C-reactive protein (CRP) (mg%)	118
Serum amylase (U/L)	1124
Serum lipase (U/L)	705
Serum triglycerides (mg/dL)	9230
Serum cholesterol (mg/dL)	308
Serum calcium/sodium/potassium (mEq/L)	8.4/135/4.8
Glucose (mg%)	449
Lactic acid dehydrogenase (LDH (IU/L)	367

After the first session, her TG was lowered by plasmapheresis from 1620 to 435 mg/dL. Her clinical condition had improved, including her respiratory failure. She was placed on an oral diet the next day and closely watched. Her CECT abdomen revealed fairly acute pancreatitis, with a Balthazar score of 7. Her oral drug regimen included atorvastatin, fenofibrate, and insulin. She was transferred from the ICU on day 7 and discharged on day 14. During her one-month visit, her TG levels were 123 mg/dL. As a result, plasmapheresis is a viable treatment option for AP caused by severe HTG and should be evaluated early in the course of treatment (11).

Case 2

A 37-year-old woman came in with a three-day history of severe epigastric discomfort as her primary complaint. Two instances of bilious vomiting accompanied the ongoing discomfort and its radiating effects on the back. She had not been using hypolipidemic medicines for the last three months, despite her doctor's advice. She was diagnosed with AP, type 2 diabetes, hypertension, and mixed dyslipidemia four years ago when she came with identical symptoms. Insulin, telmisartan, atorvastatin, fenofibrate, and a low-fat diet were the first steps in treatment. Two instances of AP occurred after she stopped therapy on her own. Laboratory parameters during the previous three presentations are depicted in Table 4. Two of her older brothers died of coronary artery disease and concomitant dyslipidemias between the ages of 40 and 45. One of the younger sisters had been diagnosed with mixed dyslipidemia and was taking medication for it.

Her vital signs were as follows: 120 beats per minute, 150/100 mmHg, 26 breaths per minute, and a body temperature of 101.40 degrees Fahrenheit. She was exhausted and dehydrated, and it showed. The epigastrium was painful and hard, and the bowel sounds were decreased, as was the liver, which was enlarged. Neutrophils made up 86% of the total leukocyte count, platelets were 220000/cm^3, and c-reactive protein was 17.2 mg/dL in the first tests. Various laboratory tests, such as those looking at lactate dehydrogenase and coagulation factors, as well as serum electrolytes, found no abnormalities. The serum was lipemic. Another set of tests found that total cholesterol was 741 mg/dL, with LDL cholesterol at 249 mg, VLDL cholesterol at 416 mg, and triglycerides at 2080 mg/dL. It was 174 mg/dL of fasting blood sugar and 286 mg/dL post-lunch blood sugar. The tail of the pancreas was visible on abdominal ultrasonography, as was a grade 1 fatty liver, as well as hepatosplenomegaly with a bulky body. Computerized tomography images showed an enlarged pancreas with smooth, edematous borders and an unidentified pancreatic duct. Also seen was fat stranding around the pancreas.

To keep the patient comfortable, intravenous fluids and painkillers were administered. Type IIb hyperlipoproteinemia (Familial Combined

Hyperlipidemia/FCHL) was diagnosed based on abnormally high triglycerides, cholesterol, and very low-density lipoprotein (VLDL) cholesterol. Fenofibrate 160 mg, atorvastatin 20 mg, and omega-3 fatty acids 2g twice a day were begun as treatment with antioxidants and omega-3 fatty acids. There was no abnormality observed in the endoscopic retrograde cholangiopancreatography. He was given insulin, antihypertensive, and hypolipidemic medications when he left the hospital (12).

HTG is a frequent clinical condition that can develop into pancreatitis if significantly increased. During the acute stages of pancreatitis, general and particular medications are available to lower triglycerides. Preventing future attacks requires proper nutrition, pharmaceutical treatment, and avoiding aggravating variables (12).

Table 4. Laboratory parameters of the patient during the previous three presentations with acute pancreatitis.

Laboratory Parameters	22 / 01 / 2007	09 / 04 / 09	26 / 03 / 2010
Triglyceride (mg/dL)	980	2074	1350
Cholesterol (mg/dL)	374	456	408
LDL cholesterol (mg/dL)	220	258	238
VLDL cholesterol (mg/dL)	104	128	97
Fasting blood sugar (mg/dL)	194	304	270
Post-lunch blood sugar (mg/dL)	317	450	380

Case 3

A 27-year-old lady in her fifth week of pregnancy was referred to the obstetrical emergency room for extreme stomach discomfort, vomiting, and fever. The epigastric discomfort was constant and spreading to the back, with supine aggravation and relief while crouching forward. Due to family HTG, her sister had a history of gestational AP. The results of her physical check-up were ordinary. There was leucocytosis and elevated TG and amylase values. The coagulation tests and other biochemical indicators were all normal. The findings on magnetic resonance imaging (MRI) were compatible with AP. Despite medical treatment, her TG did not decrease, and she was transferred to the intensive care unit (ICU) for plasmapheresis on the sixth day of her hospital stay. Fresh frozen plasma (FFP) at a volume of 40 ml per kg body weight (BW) was employed for therapeutic plasma exchange, along with heparin infusion at a rate of 10 U/kg/h for anticoagulation. The lab findings can be seen in Table 5. After three sessions, the plasmapheresis therapy was discontinued due to a considerable decline in TG. The pregnancy was terminated in the second week due to fetal loss. She was released from the hospital after eight days, with TG levels of 278 mg/dL and cholesterol levels of 181 mg/dL. She returned to the outpatient department regularly after discharge with no issues (13).

Family with familial dyslipidemia are at risk for developing pancreatitis, which HTG causes. Two- to four-fold increases in the concentration of TG in pregnant women's blood can be explained by an increase in the synthesis of Lipoproteins with a high TG content and low lipoprotein lipase activity. HTG-induced AP in pregnant women might consider plasmapheresis as an alternate, safe, and effective therapy option (13).

Table 5. Initial laboratory data of patients before the plasmapheresis treatment.

Lab findings	Case
Leucocytes (/mm3)	11200
Hemoglobin (g/dL)	9.7
Hematocrit (%)	28
Platelets (/mm3)	174000
Triglycerides (mg/dL)	2225
Amylase (U/L)	959
Lipase (U/L	-
Cholesterol (mg/dL)	470

Case 4

The patient was a 28-year-old pregnant woman with one child in this case. Even though she had not complained of nausea or vomiting, she was sent to the hospital's emergency room at 22 weeks and 6 days gestation for acute epigastric discomfort. The woman received regular prenatal care at a private clinic for her monozygotic twins. He was 70.5 kg, weighed 163.1 cm, and his vital signs were unaffected. As far as we could tell, the patient hadn't lately taken any medication.

On the other hand, her mother was being treated for hyperlipidemia and was on medicine as a result. In the upper abdomen, there was mild pain and rebound soreness. The pelvic examination revealed no signs of cervical dilation or effacement. Foetus 1 had a heartbeat rate of 152/min, whereas fetus 2 had a heartbeat rate of 158/min with a breech presentation. There was no uterine contraction or rupture of membranes. Therefore, it was determined that placental abruption and uterine rupture during the second part of pregnancy were impossible.

After high-speed centrifuging, tests were done on the patient because of lipemic blood at the emergency department. Blood tests revealed total cholesterol of 1,006 mg/dL, triglycerides of 10,392 mg/dL, low-density lipoprotein of 398 mg/dL, amylase 337 U/L, lipase 913 U/L, and blood glucose of 207 mg/dL (see Table 6). The rest of the data are as expected. In the

urine test, glucose 4+ and protein 3+ were present. AP was difficult to distinguish on abdominal ultrasonography due to the lack of visibility of the pancreas. In addition, no evidence of gallstones or cholecystitis was seen, and no other abnormalities were discovered than a somewhat obese liver. Pre-eclampsia, acute fatty liver, and pregnancy-related liver disease were ruled out based on the findings of the tests. We suspected AP. Therefore, our patient was admitted to the hospital.

Table 6. A laboratory test in Case 4.

Variable	Result	Normal range
Triglyceride	10392	28–200 mg/dL
Cholesterol	1006	120–220 mg/dL
HDL-C	18	35–88 mg/dL
LDL-C	398	0–130 mg/dL
Amylase	337	30–118 U/L
Lipase	913	6–51 U/L
AST	27	10–40 U/L
ALT	35	5–40 U/L
Creatinine	0.4	0.5–1.2 mg/dL
Sodium	114	135–145 mEq/L
Potassium	3.7	3.5–5.5 mEq/L
Chloride	85	95–110 mEq/L
Calcium	3.2	8.2–10.8 mg/dL
Glucose	207	70–100 mg/dL
Albumin	3.5	3.5–5.2 g/dL
Hemoglobin	10.9	11.5–15.5 g/dL
Leucocyte	17,850	3.7–9.5 ×103/mm3
Platelet	300,000	150–400 ×103/mm3

Note: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Within hours after being admitted, the patient began to complain about the excruciating agony he was in. As a result, the patient was given intravenous fluids, antibiotics, pain relief, insulin injections, and oxygenation. There were fetal heartbeats of 150 and 140 beats per minute. A few days later, the patient complained of significant discomfort and shortness of breath. Her consciousness began to fade as her body temperature rose to 38.2°C. Despite a respiratory rate of 60/min and tachypnea persisting, her chest X-ray was examined, but no respiratory issue was found. It was necessary to provide intravenous epinephrine and dobutamine to revive the patient after a cardiac arrest occurred due to a lack of monitoring of the patient's vital signs. When a convulsion occurred shortly after this, anticonvulsant medicine $MgSO_4$ was administered. Afterward, blood pressure readings of 70/40 mmHg, pulse rate of 134 beats per minute, and respiration rate of 25 beats per minute revealed that she had regained consciousness. However, she was in a state of stupor. Neither of the two babies had a heartbeat, and intrauterine fetal death had been established. Glycemic levels had risen to 474 mg/dL, amylase levels had risen to 1,833 U/L, and lipase levels had risen to 1,863. HTG is thought to have triggered AP, necrotizing cells in the pancreas that led to the onset of diabetic ketoacidosis, which in turn led to cardiac arrest. The patient's excessive triglyceride level prevented extracorporeal membrane oxygenation, which proved unsuccessful. As a result, the patient's blood pressure collapsed and he died just 24 hours after being admitted (14).

It is estimated that just three in every 10,000 pregnancies will result in an AP. While it can occur at any point in the pregnancy, most instances (52 percent) occur in the third and postpartum trimesters. When increased oestrogen levels bring on HTG in the womb, it can cause AP, which can be fatal to both mother and child. This has been seen in cases where pregnant women died at 23 weeks of gestation from AP brought on by an exacerbation of HTG-induced AP (14).

Case 5

Epigastric discomfort, nausea, and reduced oral intake were described in a 40-year-old Caucasian guy with a history of hyperlipidemia type III, coronary artery disease (CAD), peripheral vascular disease (PVD), hypertension, type 2 diabetes mellitus. The physical examination revealed tachycardia up to 100 beats per minute, discomfort in the epigastrium, and xanthomas with striae palmaris in the hands. There was a moderately increased lipase of 334 U/L (reference range 114-286 U/L) and an elevated TG level of 45.3 g/L in the lab results (reference range 0-149). The pancreas had considerable fat stranding on an abdominal CT scan, and the pseudocyst was stable. He was put on a drip of insulin at a dosage of one unit every hour. TG levels dropped to 9.57 g/L following three days of insulin infusion. Despite this, the patient's symptoms persisted, including severe stomach discomfort and an inability to swallow. After three days in the hospital, the patient had his first apheresis session. The patient's symptoms improved, and he could tolerate oral intake after 24 hours of apheresis. Apheresis reduced triglyceride levels to 4.61 g/L after 24 hours, and they were 6.75 g/L on discharge day.

Maintaining bi-monthly maintenance apheresis operations as an outpatient was decided upon due to the patient's severe cardiac history and the fact that this was the second time in a year that he had presented with HTGP. A prescription for hydrochlorothiazide was given at home with the patient., 75mg Plavix, 325mg aspirin, 50mg BID metoprolol tartrate (a beta-blocker), 80mg atorvastatin (a statin), 200mg fenofibrate (an omega-3

polyunsaturated fatty acid). Recurrent pancreatitis led to three hospitalizations over 12 months, one of which was related to adherence issues with apheresis, a fat-free diet, and lipid-lowering drugs. His TG levels were generally far below 15 g/L. After 12 months, the pseudocyst had completely disappeared from the abdomen, and there were no signs of any further issues (15).

Following effective treatment of HTG-AP in a guy with HTG type III, bi-monthly outpatient apheresis management therapy sessions were instituted to prevent future HTG-Aps (15).

Declarations

Author Informations

Ramandeep Singh
Affiliation: Department of Pharmacy, Himachal Institute of Pharmacy, Dental College Campus, Himachal Pradesh, India..
Contribution: Conceptualization, Data Curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - Original Draft, Writing - Review & Editing.

Ranjodh Jeet Singh
Affiliation: Department of Pharmacology, Maharishi Markandeshwar institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.
Contribution: Conceptualization, Data Curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - Original Draft, Writing - Review & Editing.

Satinder Kakar
Affiliation: Department of Pharmacy, Himachal Institute of Pharmacy, Dental College Campus, Himachal Pradesh, India.
Contribution: Conceptualization, Data Curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - Original Draft, Writing - Review & Editing.

Jasmeet Kaur
Affiliation: Department of Pharmacy, Himachal Institute of Pharmacy, Dental College Campus, Himachal Pradesh, India.
Contribution: Conceptualization, Data Curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - Original Draft, Writing - Review & Editing.

Conflict of Interest

The authors declare no conflicting interest.

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The unpublished data is available upon request to the corresponding author.

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